the presence of the N-methyl group provides compounds which have improved activity, and/or toxicity, and/or stability as compared to the compounds disclosed by Kobrehel, et al.

Along these lines, attached hereto are Tables 3-7, Figure 1 and accompanying Declaration. These represent testing of compound of the present invention (N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A) and comparison of such to erythromycin A and the starting 11-aza-10-deoxo-10-dihydroerythromycin A, respectively. These tests provide the side-by-side comparisons requested by the Examiner in paragraph 5 of page 2 of the Office Action. These tests have been provided to overcome the Examiner's criticism of the prior tests presented. Such were not presented earlier since it was believed that the prior tests presented were sufficient to demonstrate the patentability of the present invention. The N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A invention which is the closest of the compounds of the present invention to the prior art.

With respect to the attached tests, in order to measure the in vitro potency of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A, the compound was tested in comparison with erythromycin A and its 11-aza derivative against 391 clinical isolates, i.e. 182 gram-positive (Table 3), 179 gram-negative (Table 4) and 30 anaerobic bacterial organisms (Table 5). In vitro, N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A showed generally against gram-positive isolates similar antibacterial spectra to erythromycin A and its 11-aza derivative. However, against gram-negative strains it was 2-5-fold more active than erythromycin A and in therapeutic concentrations of 0.5-4.0 mcg/ml inhibited about 30% more strains than the starting 11-aza-10-deoxo-10-dihydroerythromycin A. Out of 179

gram-negative organisms 64 (35.8%) were resistant to erythromycin A, 22 (12.3%) to 11-aza-10-deoxo-10-dihydroerythromycin A and only 6 (3.4%) to the N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A of the present invention.

On examination of acute toxicity in mice by the method of Litchfield-Wilcoxon, it has been found that N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A is less toxic than erythromycin A or the 11-aza-10-deoxo-10-dihydroerythromycin A (Table 6).

The acid stability of some of the newly prepared compounds of the present invention and the parent antibiotic erythromycin A are summarized in Table 7. All compounds were exposed to hydrochloric acid (pH 1.2) and the remaining activity was determined by the two-fold dilution technique vs. Staphylococcus aureus ATCC 6538-P. The results are given as the minimal inhibitory concentrations (MIC) in mcg/ml. The N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A and its derivatives were more stable in acidic medium at pH 1.2 than erythromycin A.

After oral administration to rabbits, blood levels of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A(1) were higher and more prolonged than those of the erythromycin base (Figure 1).

Accordingly, in view of the above discussed showing and the tests presented in our response to the previous office action, it is quite evident that the compounds of the present invention exhibit pharmaceutical properties which are superior to and not predictable from the prior art. Therefore, the compounds of the present invention are non-obvious and are patentable. See In re Papesch 137 USPQ 43.

In conclusion, it is believed that each of the claims in this application is definite and clear. It is further believed that the reasons why the present invention distinguishes over the prior art have been fully set forth. Reconsideration and allowance are therefore respectfully solicited. If the Examiner thinks that an interview might serve to advance the prosecution of this case in any way, the undersigned attorney is available at the telephone number noted below.

Respectfully submitted,

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